BERYLLIUM DISEASE

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INTRODUCTION

Acute and chronic beryllium disease is caused by exposure to beryllium compounds.

Acute beryllium disease, the acute response to inhaling toxic beryllium compounds, is defined as disease which lasts less than one year, occurs during exposure to beryllium, and includes any or all of the following: nasopharyngitis, tracheitis, bronchitis, pneumonitis, dermatitis, and conjunctivitis.

Chronic beryllium disease is caused by inhalation of beryllium, lasts longer than one year, and usually causes both systemic and pulmonary abnormalities.

A separate disease form is subcutaneous granulomas secondary to direct implantation of beryllium compounds in the skin.

The term berylliosis will not be used in this report, because confusion has resulted from that terminology. Hardy and Chamberlin have noted that the word berylliosis implies two false conclusions: beryl ore itself causes disease and beryllium disease is similar to dust diseases of the lung (the pneumoconioses) (8).

CAUSATIVE AGENTS

The experience of the Beryllium Case Registry since 1952 and the data from many published reports of beryllium disease occurring in workers, support the conclusion that beryllium metal and all forms of beryllium, excluding beryl ore, have been associated with disease in humans.

Stokinger concluded that "chronic respiratory disease has occurred in connection with almost every major type of beryllium manufacture and use" (26). More recently, Hamilton and Hardy summarized 22 years of data from the Beryllium Case Registry and concluded that beryllium metal and all beryllium compounds, except beryl ore, have caused disease (7). Previous studies have emphasized the difference in disease potential between beryllium compounds associated with chronic or with acute disease. For acute disease, the more soluble beryllium compounds, including beryllium fluoride, beryllium sulfate, and ammonium beryllium fluoride, have been implicated as the cause of both upper and lower respiratory abnormalities. In addition, acute pneumonitis has been associated with beryllium oxide, carbide, oxyfluoride, hydroxide, and zinc beryllium silicate. For chronic beryllium disease, beryllium oxide, beryllium phosphors, and beryllium copper alloys have been implicated.

However, these categorizations have been confused by the fact that almost all beryllium operations can produce more than one form of airborne beryllium. Based on current knowledge, therefore, all beryllium compounds except beryl ore should be considered potentially harmful.

OCCUPATIONS AND INDUSTRIES USING BERYLLIUM

1. Mining*
2. Extraction of beryllium
3. Beryllium metallurgy
4. Production and use of beryllium alloys
   a. Beryllium copper alloys—springs, diaphragms, electrical contacts, connectors in electronics and data processing equipment, bearings, gears, airplane engine parts, precision castings, molds, antispark tools, welding electrodes and fixtures
   b. Beryllium nickel alloys—instrument diaphragms, high-temperature springs, matrices of diamond drill bits, fuel pumps, dies for shaping
   c. Dental alloys—nickel, chromium, beryllium

*To date, no cases of beryllium disease have been identified from mining operations.

d. Other alloys (including aluminum, magnesium, and platinum)

5. Computers
6. Beryllium ceramics manufacturing—crucibles, spark plugs, bricks, thermal coatings, rocket motor parts, nose cones
7. X-ray tube window manufacturing
8. Electronic equipment manufacturing
9. Nuclear reactor manufacturing
10. Atomic energy development and research
11. Guidance and navigation systems manufacturing (gyroscope housings)
12. Rocket parts, heat shields, instruments
13. Gas mantle manufacturing
14. Rocket fuel development research
15. Salvage of fluorescent and neon lamps
16. Nonferrous foundry products
17. Tool and die manufacturing

EPIDEMIOLOGY

Information concerning the occurrence and distribution of beryllium disease in populations exposed to this material is available from several sources. Studies of beryllium extraction and fluorescent lamp workers in the 1940's, analyses of neighborhood cases, studies of working populations exposed to beryllium after 1950, and Beryllium Case Registry data from over 890 cases of beryllium disease are major epidemiologic sources.

Beryllium disease prevalence data derived from working populations before 1950 are of limited value. Studies of workers exposed to beryllium prior to 1950 were concerned with exposures which were different in type and intensity from modern exposures. After 1950, beryllium disease cases decreased markedly in association with generally reduced beryllium air concentrations in the workplace. Therefore, information on disease prevalence derived from studies of extraction or alloy workers prior to 1950 is not comparable with that obtained after 1950 for the same operations. Another working group studied previously was fluorescent lamp production workers. Beryllium was discontinued from use for that purpose in 1950. All studies have been affected by the fact that beryllium disease may develop 20 to 25 years after the last known exposure to beryllium. To the author's knowledge, published reports of long-term longitudinal follow-up of entire plant populations exposed before 1950 are not available. The high rate of worker turnover during World War II frequently limited exact information about the total population at risk from exposure in many studies. Therefore, limited conclusions can be drawn from studies published in 1950 and reviewed by Tepper, et al., citing prevalence rates (mainly, acute beryllium disease) of 0.3% in the extraction industries, 2% in the beryllium copper alloy industry, and 3% in a fluorescent lamp plant (27).

Another study cited by Tepper et al. reported on the occurrence of beryllium disease in a total of 1,850 exposed persons in an extraction plant (27). Employees' health records were analyzed over an eight-year time period from 1940 to 1948. Results showed that 7% of the workers developed acute beryllium disease and 0.9% chronic disease. In another group of 191 workers in a research facility using beryllium, the rates for acute and chronic disease during that 8-year period were 3.7% and 4.2% respectively.

Beryllium disease has been reported in patients with no known occupational exposure to beryllium, but who lived near a plant or industry utilizing beryllium. A report by Eisenbud et al. described 11 patients with chronic beryllium disease of nonoccupational etiology living in the vicinity of a beryllium extraction plant (4). Ten of 11 cases lived within 0.75 miles of the plant, suggesting community exposure from plant discharges into the air. Results of air concentration measurements of beryllium at locations surrounding the plant provided information for the community air beryllium threshold limit value of $0.01\mu m/m_3$. Tepper et al. reviewed 47 cases of neighborhood chronic beryllium disease listed with the Beryllium Case Registry and found that 24 had been exposed to beryllium-contaminated clothing at home, 13 had only lived near a plant utilizing beryllium, 8 had both lived near a plant and had exposure to contaminated clothing, and in 2 cases the exposure source remained unknown (27). These data suggest that both contaminated work clothes and community pollution with beryllium-containing air from stack discharges account for neighborhood cases of chronic beryllium disease.

Recent data from the Beryllium Case Registry indicate the prevalence of neighborhood cases has decreased since 1949 due to control measures. Of 672 cases exposed to beryllium

before 1949, 11% were reported by Hasan and Kazemi as neighborhood cases in contrast to 3% in 36 cases exposed after 1949 (10). Of the 55 cases admitted to the Beryllium Case Registry from 1973 to 1977 and reported by Sprince and Kazemi, only one was a neighborhood case (22).

Current information concerning prevalence and distribution of chronic beryllium disease in working populations exposed after 1950 is available from several studies. Kanarek et al. reported the results of a medical and environmental survey at one beryllium extraction and processing plant in Pennsylvania (12). They found that 14% of 214 employees surveyed had the radiographic abnormality indicative of interstitial pulmonary disease and 5% had both interstitial disease on x-ray and hypoxemia (Pa_{O_2} < 80 mmHg), probably secondary to beryllium disease. These abnormalities were found in association with some peak air concentrations of beryllium in that workplace exceeding 50 times the accepted peak threshold limit value (TLV) of 25 $\mu g/m^3$. Four workers from this plant were admitted to the Beryllium Case Registry, having met the criteria for the diagnosis of chronic beryllium disease.

Follow-up study at that plant three years later reported by Sprince et al. revealed that peak air concentrations of beryllium were reduced to below 25 $\mu g/m^3$ throughout the plant and that improvements in hypoxemia and interstitial disease (radiographically) occurred in some workers who had continued to work at the plant and had received no medical treatment (21).

A 1977 survey in a beryllium-copper alloy production plant in Pennsylvania (unpublished data) revealed that, of 305 workers surveyed, 3 workers (1%) met diagnostic criteria for chronic beryllium disease and were admitted to the Beryllium Case Registry. A total of 8 workers —2.6% of the work force surveyed—were found to have interstitial disease on x-ray, probably related to beryllium inhalation.

A study from Britain by Coates et al. reported that 3 of approximately 130 beryllium production workers followed for 25 years (1952-1977) developed chronic beryllium disease, and 2 others had an episode of acute pneumonitis secondary to beryllium exposure (2).

Although these studies point to a low prevalence of chronic beryllium disease in current working populations, the true prevalence of beryllium disease is most likely higher. Retired employees, patients lost to medical follow-up, and individuals who develop beryllium disease after the well-documented (possible) latent period of up to 25 years between exposure and onset of disease, are not included in results obtained from the active work force.

The other source of information is the Beryllium Case Registry (BCR) which was established at the Massachusetts General Hospital in 1952 by Dr. Harriet L. Hardy. The main purpose of the BCR was to collect medical information and exposure data from patients in the United States with beryllium disease, to study the course and complications of this disease, and to establish criteria for the diagnosis of beryllium disease. The BCR has continued those studies and currently has on file 892 cases of patients with beryllium disease: 636 with chronic disease, 212 with acute disease, and 44 who developed chronic disease after having one or more episodes of acute disease. Of the total, 408 are known to be dead, 361 are known to be alive, and in 123 cases, the status was unknown at last follow-up in 1978. Sprince and Kazemi have reported approximately 10 to 12 new cases admitted to the BCR annually for the past five years, 40% of whom had initial exposure to beryllium after 1950 (20). Sources of exposure of recent cases are summarized in Table II-25.

Although 892 represents the total number of cases reported to the BCR from 1952 to 1978, this number is most likely an underestimate of actual disease prevalence because 1) physicians unfamiliar with this uncommon disease frequently do not consider it as a diagnostic possibility; 2) recognized difficulty exists in differentiating beryllium disease from other pulmonary granulomatous diseases, especially sarcoidosis; and 3) large numbers of patients with recognized beryllium disease have not been reported to the BCR.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The population at risk for beryllium disease in the workplace includes workers engaged in all operations producing or using beryllium and its compounds, excluding beryl ore mining. Exposures also occur in operations which involve melting, casting, grinding, machining, and drilling of beryllium-containing products. A U.S. Public Health Service Survey in 1970 estimated that at least 30,000 working people could have potential exposure to beryllium by inhalation.

Table II-25

BERYLLIUM CASE REGISTRY—
CASE ENTRIES 1973-1978
SOURCE OF EXPOSURE

1.	Extraction and smelting	7
2.	Beryllium metal production	30
	A. alloys	18
	B. ceramics	3
	C. x-ray tubes	2
	D. research (atomic)	6
	E. vacuum tube	1
3.	Fluorescent tube production	17
4.	Neon tube production	1
5.	Neighborhood cases	1
6.	Unknown	4
		60*

*Of the 60 total cases, 43 were men, 17 women. Initial exposure to beryllium occurred before 1950 in 37 cases, after 1950 in 23 cases.

However, the recent National Occupational Hazard Survey, looking at exposure to beryllium and beryllium oxide, estimated that 21,233 people in 2,019 plants had potential exposure to beryllium and 855,542 people in 93,132 plants had potential exposure to beryllium oxide. Since results of these two surveys are widely divergent, further investigations are required to determine which is accurate.

The scientific basis for an estimate of disease prevalence has been summarized in the preceding section, Epidemiology, page 386.

PATHOLOGY AND PATHOGENESIS

Freiman and Hardy studied the histopathology in lung specimens for 130 cases of chronic beryllium disease from the Beryllium Case Registry (5). Six cases were acute and 124 chronic disease. Their observations have provided a useful pathologic categorization for chronic beryllium disease and correlation between histopathologic changes and clinical course.

Their description of the changes in six patients who died of acute disease was that of nonspecific acute and subacute bronchitis and pneumonitis. Interstitial and intra-alveolar edema, alveolar cell proliferation and desquamation, cellular infiltration with lymphocytes and plasma cells, hyaline membranes, and organizing pneumonia were important features. No associations between type or severity of these changes and the known clinical manifestations could be made.

Characteristic changes of chronic beryllium disease are those of chronic interstitial pneumonitis with noncaseating granulomas. Histiocytes, lymphocytes, and plasma cells comprise the cellular infiltrates. Giant cells, asteroid bodies, and calcific inclusions in granulomas are seen frequently.

Chronic cases were divided into Groups IA, IB, and II based on granuloma formation and cellular infiltration (Table II-26). Eighty percent of cases were in Group I and 20% in Group II. Histopathology in Group II was indistinguishable from that observed in sarcoidosis and was associated with a better prognosis and a better response to steroid treatment, compared with Group I (A and B) patients. Fibrosis was present in a large proportion of cases and was variable in degree in different parts of the lung.

Noncaseating granulomas have also been found in lymph nodes, liver, skin, spleen, and other tissues. Representative histopathology from lung and mediastinal lymph nodes is shown in Figures II-38 and II-39.

In animal experiments using several different species, beryllium has been found to be toxic by all routes of administration including intravenous, inhalation and tracheal instillation, intraperitoneal, and subcutaneous instillation. Toxicity by the oral route has been found to be low. Both acute pneumonitis and chronic pulmonary granulomatous disease have been produced in experimental animals exposed to beryllium.

In humans, the disease is caused by inhaling beryllium in all forms with the exception of beryl ore, which has not caused beryllium disease.

The mechanism of action of beryllium in producing acute respiratory tract disease is most likely that of direct toxic effect on mucosal surfaces, causing edema, inflammation, and necrosis. The pathogenesis of the chronic disease is not certain, although a suggested mechanism is that beryllium combines with immunoglobulins, causing the release of toxic substances and subsequent transport of a protein-beryllium complex to extrapulmonary tissues. Beryllium is

Table II-26

HISTOLOGICAL CLASSIFICATION OF CHRONIC BERYLLIUM DISEASE

Histological Characteristics	Subgroup 1A	Subgroup 1B	Group II
Interstitial cellular infiltration	Moderate to marked		Slight or absent
Granuloma formation	Poorly formed or absent	Well formed	Numerous and well formed
Calcific inclusions	Variable; frequently present and numerous		Few or absent

Source: Freiman and Hardy (5)

distributed widely in the body and has been found in many organs and tissues. Excretion is slow and by the renal route. Beryllium may be detected in urine up to 20 years after a patient's last known beryllium exposure.

Immunologic and hypersensitivity mechanisms in the pathogenesis of chronic beryllium disease have been proposed by several investigators. Deodhar et al. studied blast transformation of lymphocytes in the presence of beryllium sulfate (in tissue culture) from patients with chronic beryllium disease, exposed healthy workers, unexposed healthy controls, and patients with other lung diseases (3). Strongly positive (3 or 4+) results were found in 60% of patients with chronic beryllium disease and in only one healthy, unexposed control. The authors indicated a good correlation between severity of disease and amount of lymphocyte transformation. Preuss reported the usefulness of blast transformation of lymphocytes in separating groups of patients with chronic beryllium disease from those with sarcoidosis (18). Price et al. reported results of the beryllium macrophage migration inhibition test in 5 patients with chronic beryllium disease, 20 healthy controls, and 50 healthy beryllium workers (19). They demonstrated the production of a macrophage migration inhibition factor from lymphocytes in the 2 patients with chronic beryllium disease not receiving steroids, in 7 healthy beryllium workers presumed to be sensitized to beryllium, and in none of the controls. These studies suggest that cell-mediated immunity to beryllium is involved in the generation of tissue changes in chronic beryllium disease. This is also compatible with observed histologic changes.

CLINICAL DESCRIPTION

Symptoms and Signs

Clinical manifestations of beryllium disease are divided into acute and chronic effects of beryllium exposure. Acute disease has been defined as those beryllium-related conditions that last for less than one year and occur during exposure to beryllium. Acute disease is dose-related and similar to acute tracheobronchitis or pneumonitis caused by the irritant gases. Chronic disease lasts longer than one year and, although patients may develop the disease during beryllium exposure, the onset of disease may follow cessation of exposure by weeks to years. The chronic disease is a pulmonary and systemic granulomatous disease for which no dose-response relationship has been established.

Acute dermatologic manifestations include dermatitis appearing one to two weeks after initial exposure to soluble salts of beryllium and associated with a positive skin patch test to soluble beryllium compounds. A hypersensitivity mechanism has been generally accepted for this disease form because of the observed latent period between exposure and onset; skin patch test reactions; and reports of subsequent dermatitis in previously sensitized individuals, appearing more rapidly and after less intensive exposure. After exposure ceases, the dermatitis resolves usually within two weeks. Immediate reactions of dermatitis may occur in previously

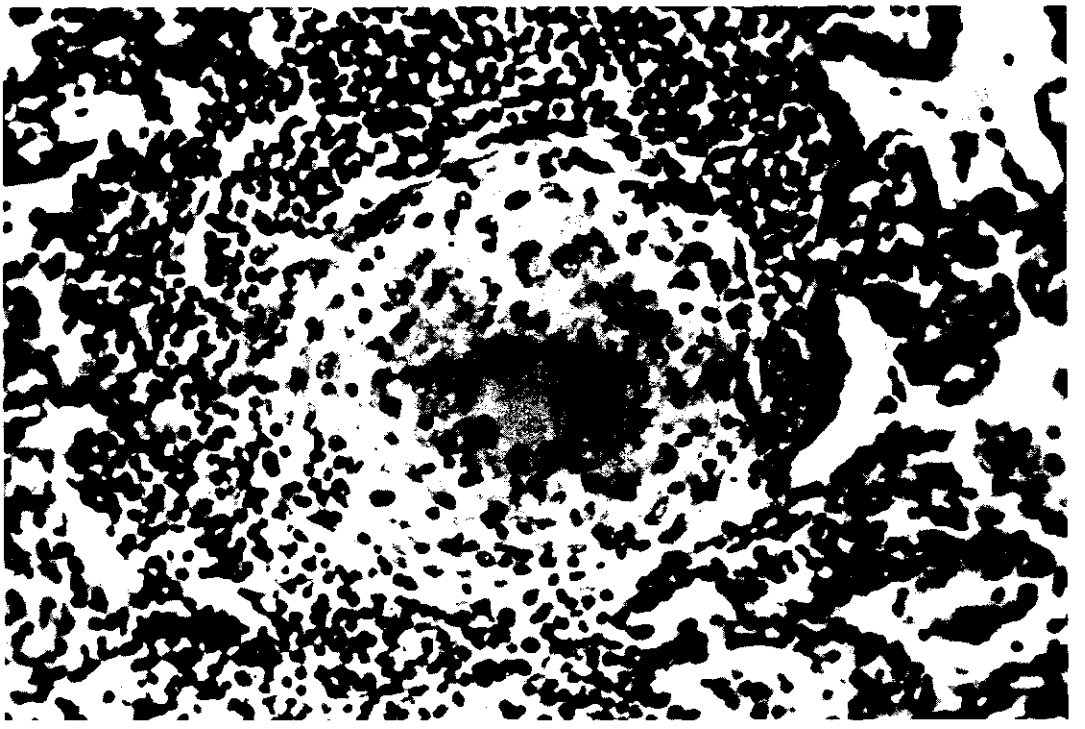

Figure II-38. Chronic beryllium disease, lung, Group IB. This biopsy specimen shows marked interstitial cellular infiltration and a well-formed granuloma containing a giant cell.

unexposed patients and are related to primary irritation, secondary to a high concentration of beryllium exposure on the skin. Conjunctivitis, periorbital edema, and upper respiratory tract involvement may accompany dermatitis.

Localized skin ulceration secondary to beryllium contamination of a wound or direct implantation of beryllium into the skin have been reported in the past. Healing usually requires removal of beryllium from the ulcer.

Acute nasopharyngitis has been associated with beryllium exposure. Symptoms include pain, swelling, bleeding of the nose and pharynx; objective signs include edema, hyperemia, and bleeding points. Fissures and ulcerations occur in untreated cases. Three to six weeks after exposure ceases, nasopharyngitis has usually resolved.

Acute tracheobronchitis secondary to beryllium exposure has been observed. Onset and course of this clinical pattern may be severe and rapid or subacute and slower, depending on the level of exposure. Symptoms are chest discomfort, nonproductive cough, and dyspnea. Physical findings include hyperemia of the upper respiratory tract and rhonchi and rales on auscultation of the chest. Increased bronchovascular markings have been described on chest x-ray. Therapy is cessation of exposure and bedrest; recovery is usually complete within one month.

Acute chemical pneumonitis is the most serious of acute diseases related to beryllium exposure. Chemical pneumonitis secondary to beryllium exposure may be severe and fulminant after brief exposure to very high concentrations of beryllium or more subacute in onset and course after prolonged exposure to lower concentrations. Fatal cases are rare; resolution is generally complete by six months. Symptoms and signs are similar to those found with other causes of chemical pneumonitis. Symptoms are dyspnea, cough and substernal pain. Blood-tinged sputum, weight loss, and fatigue have been reported associated symptoms. Physical signs are tachypnea, tachycardia, rales, and cyanosis in severe cases. Radiographic findings are diffuse or localized infiltrates or haziness of lung fields. Laboratory findings are unremarkable. Reduced lung volumes and hypoxemia characterize acute pneumonitis. Therapy is determined by the disease's severity. Bedrest, observation for

Figure II-39. Chronic beryllium disease, mediastinal lymph node. This biopsy specimen shows some well-formed granulomas and intense cellular infiltration.

pulmonary edema, and supplemental oxygen and corticosteroids (if indicated) are recommended therapy modes.

Acute beryllium disease is currently rare. In the last six years, only one case of acute beryllium disease has been reported to the Beryllium Case Registry. Out of 892 cases of beryllium disease on file with the Beryllium Case Registry, 212 represent acute disease. According to Registry data, approximately 17% of patients with acute disease have developed chronic disease. Factors accounting for the occurrence of chronic disease in individuals who have had previous acute disease are unknown at present.

Chronic beryllium disease is the pulmonary and systemic granulomatous disease caused by beryllium exposure. The duration of exposure in reported cases is generally several months to years. The latent period between initial exposure and onset of disease is variable but averages 10 to 15 years. Disease may occur while a patient is still exposed to beryllium or may follow cessation of exposure by up to 25 years.

The severity of disease varies from an asymptomatic patient with only radiographic abnormalities to severely disabled patients with chronic respiratory failure and cor pulmonale. The lungs are almost invariably affected. A report by Stoeckle et al. of 60 patients with chronic beryllium disease indicated that 95% had dyspnea, the most frequent symptom (25). A recent review of BCR data by Hasan and Kazemi indicated in 76 cases, exertional dyspnea was the most common presenting symptom followed in frequency by cough, fatigue, weight loss, and chest pain (10). Unusual initial symptoms were arthralgias, fever, orthopnea, anorexia, hemoptysis, palpitations, convulsions, wheezing, nausea, vomiting, and hoarseness.

Results of physical examination vary. Abnormalities include bibasilar rales; accentuation of the pulmonic component of the second heart sound if pulmonary hypertension is present; peripheral lymphadenopathy, skin lesions, hepatosplenomegaly, and clubbing. Signs of cor pulmonale may occur in long-standing, advanced cases. Parotid gland enlargement has been reported in one patient with chronic beryllium disease (10). The physical examination may also be entirely normal in chronic beryllium disease.

Clinical Course

The collected experience of clinicians following patients listed with the Beryllium Case Registry has been that chronic beryllium disease follows a variable clinical course. Some patients have a stable course for many years followed by eventual deterioration. Patients with radiographic abnormalities and no symptoms may have a stable course or develop symptoms after a variable time. There are reports of numbers of patients who have improved without treatment. One case of complete resolution of symptoms, signs, and nodules on chest x-ray, temporally related to adrenocorticotrophin (ACTH) therapy, has been reported by Stoeckle et al. (25). Although results of controlled trials are not available, it is the impression of clinicians who have followed large numbers of patients with chronic beryllium disease that corticosteroid therapy improves symptoms, signs, clinical course, and radiographic abnormalities in many treated cases. Early improvements in lung function (including lung volumes and alveolar-arterial oxygen tension differences ($A\text{-}aD_{O_2}$) at rest) have been reported by Gaensler et al. in patients treated with corticosteroids, although improvement was not sustained (6). There is an indication that the pattern of lung function abnormality may affect the clinical course. A study by Andrews et al. of lung function in 41 patients with chronic beryllium disease revealed three patterns of abnormalities: restrictive, obstructive, and interstitial defects (1). The last group comprised 36% of the cases and was characterized by reduced carbon monoxide diffusing capacity, widened $A\text{-}aD_{O_2}$ at rest, and exercise hypoxemia. That group had the least deterioration of function five years later compared with the obstructive and restrictive groups. Almost all patients in the groups were receiving chronic corticosteroid therapy.

A recent longitudinal study of beryllium production and extraction workers at one plant suggested that medical surveillance programs of currently exposed workers may be used to detect beryllium disease at an early stage and that the disease may be reversible when beryllium air concentrations are lowered (12)(21). The initial observations of those workers showed that 14% had interstitial abnormalities on chest x-ray, 9% had hypoxemia, and 5% had both hypoxemia and interstitial infiltrates at a time when peak beryllium air concentrations were elevated above the peak acceptable level of 25 mg/m^3 in 60% of samples taken. Three years later, after peak air concentrations were all lowered to less than 25 mg/m^3, workers had improvements in hypoxemia and resolution of interstitial infiltrates even though none had received therapy, stopped smoking, or changed jobs. Six years after the initial survey, peak air concentrations of beryllium were still lower and further radiographic resolutions were noted by Sprince et al. (20).

Laboratory Investigations

Pulmonary Function Tests

Early reports of lung function changes in chronic beryllium disease emphasized a restrictive defect characterized by reduction in lung volumes, normal airflow rates, hypoxemia at rest (exacerbated by exercise), and reduced diffusing capacity for carbon monoxide. More recent data from the Beryllium Case Registry reported by Andrews et al. showed that of 41 patients with chronic beryllium disease, only 20% had a restrictive defect, while 39% had an obstructive pattern, 36% an interstitial defect, and 5% were normal (1). Table II-27 summarizes lung function abnormalities associated with the three groups. The obstructive pattern, which occurs in both smokers and nonsmokers, is associated with peribronchial location of granulomas. Prognosis was best for the interstitial group, which showed very little deterioration at five-year mean follow-up; it was worse for the obstructive and restrictive groups, both of which showed worsening of physiologic impairment in spite of continued corticosteroid therapy. Cor pulmonale was frequent in the obstructive group. A recent study by Kanarek et al. suggests that mild interstitial disease, secondary to beryllium exposure, may only be characterized by mild hypoxemia and mild increase in $A\text{-}aD_{O_2}$ (12).

Radiologic Studies

Typical radiographic features in chronic beryllium disease are diffuse infiltrates and bilateral hilar lymphadenopathy (see Figure II-40). These abnormalities are not diagnostic for chronic beryllium disease and similar changes occur in sarcoidosis, silicosis, and some cases of tuberculosis. The radiographic densities have been classified as granular (which measure up to 1 mm in diameter), nodular (1 mm to 5 mm in diameter), and linear. Mixed patterns of den-

Table II-27

CRITERIA FOR CLASSIFYING LUNG FUNCTION TESTS IN CHRONIC BERYLLIUM DISEASE

Type of Defect	Lung Function Criteria for Group
Interstitial	1. Normal ventilation and lung volumes 2. Carbon monoxide diffusing capacity less than 80% of predicted
Restrictive	1. Vital capacity less than 80% of predicted 2. Normal Forced Expiratory Volume in 1 second (FEV_1) 3. Total lung capacity (TLC) less than 80% predicted
Obstructive	Three of the following: 1. FEV_1 less than 72% 2. Peak expiratory flow rate less than 80% of predicted 3. Maximum breathing capacity (MBC) less than 80% of predicted 4. Residual volume/total lung capacity (RV/TLC ratio) greater than 30% 5. Helium equilibration time greater than 2.5 min.

Source: Andrews, Kazemi, and Hardy (1).

sities may occur, and densities may increase, diminish, or remain stable. In a recent Beryllium Case Registry review of 69 patients' radiographic patterns by Hasan and Kazemi, a mixed pattern with granular, nodular, and linear densities was observed most frequently (36%). This was followed by a mixed pattern with fibrosis in 30%, a nodular pattern in 14%, and granular densities in 6% (10). Among those patients, 35% had hilar lymphadenopathy, and in 83% of those, the enlargement was bilateral. Hilar enlargement has been described in 45% of another series of 60 Beryllium Case Registry patients reported by Stoeckle et al. (25). Hilar adenopathy alone, without parenchymal lesions, is rarely the presenting feature of chronic beryllium disease. The radiographs of one patient with this uncommon presentation who went on to develop interstitial infiltrates are shown in Figures II-41 and II-42. Calcification of pulmonary densities and hilar lymph nodes has been reported by Stoeckle et al. (25). Pleural thickening, cysts, a single nodule, and pneumothorax have been reported but are uncommon. Contraction of upper lobes with hyperinflation of lower lobes has been found in long standing cases.

Other Laboratory Abnormalities

Hypergammaglobulinemia (mainly IgG or IgA), elevated erythrocyte sedimentation rate, and erythrocytosis may be seen in patients with chronic beryllium disease. Hyperuricemia, hypercalciuria, and hypercalcemia are associated laboratory abnormalities in some patients.

Associated Abnormalities

Chronic beryllium disease is associated with extrapulmonary abnormalities in most cases.

This histopathology is usually noncaseating granulomas with the finding of elevated beryllium content in these extrapulmonary tissues. Thoracic and other lymph nodes may be involved and a report by Hasan and Kazemi has shown markedly elevated beryllium content in chronic beryllium disease in mediastinal lymph nodes (10).

Skin involvement associated with chronic beryllium disease (and not as a result of contact dermatitis or direct implantation of beryllium on the skin) is that of nodular lesions showing noncaseating granulomas when biopsied. Hepatosplenomegaly has been observed in 11% of patients and noncaseating granulomas have been found on liver biopsy.

Figure II-40. Chest radiograph showing typical features of chronic beryllium disease, namely diffuse interstitial densities and bilateral hilar lymphadenopathy.

Renal calculi have been reported in 3% to 7% of patients with chronic beryllium disease. Hypercalcemia has been observed in 1% to 4% of patients and hypercalciuria in 1% to 20%. The mechanisms for renal stone formation and abnormalities in calcium metabolism are unknown at present.

Hyperuricemia, probably secondary to impaired renal clearance of uric acid, was reported by Kelley et al. in 6 of 15 patients with chronic beryllium disease (14).

Rare manifestations of chronic beryllium disease include parotid gland enlargement, central nervous system granulomas and restrictive cardiomyopathy reported by Sprince et al. (24).

Treatment

The only available therapy for chronic beryllium disease is corticosteroids. In some cases, clinical impressions are that therapy may alter the course of the disease favorably, although no long-term cures have been reported. Lifetime therapy with an oral corticosteroid is usually required and exacerbations of symptoms and radiographic abnormalities have been reported after withdrawal of corticosteroids.

As in other chronic pulmonary diseases, supplemental oxygen therapy may improve hypoxemia and should be considered in patients who develop significant hypoxemia. Therapeutic modalities which may be useful for complicating right heart failure and pulmonary hypertension include supplemental oxygen for severe hypoxemia, diuretics, and possibly digitalis. Prevention of serious bacterial and viral infections is also important. To that end, antibiotic therapy for suspected acute bacterial tracheobronchitis and immunizations to prevent influenzal and pneumoconial infections should be employed.

Prognosis

The variable clinical course has been outlined in a previous section. To date, 41% of the 892 patients listed with the Beryllium Case Registry are known to be deceased.

DIAGNOSTIC CRITERIA

The diagnosis of beryllium disease is based on consistent radiographic, physiologic, and histopathologic features in a patient with documented significant exposure to beryllium. Investigators working with the Beryllium Case Registry have established six criteria for the

Table II-28

CRITERIA FOR THE DIAGNOSIS OF BERYLLIUM DISEASE

1. Establishment of significant beryllium exposure based on sound epidemiologic history
2. Objective evidence of lower respiratory tract disease and a clinical course consistent with beryllium disease
3. Chest x-ray films with radiologic evidence of interstitial fibronodular disease
4. Evidence of restrictive or obstructive defect or diminished carbon monoxide diffusing capacity
5. Pathologic changes consistent with beryllium disease on examination of lung tissue and/or thoracic lymph nodes
6. Presence of beryllium in lung tissue or thoracic lymph nodes or other tissues or the presence of beryllium in a urine specimen

Source: Kazemi (13)

diagnosis of chronic beryllium disease, based on collected information from hundreds of cases of the disease since the Registry was established in 1952. These criteria are presented in Table II-28. To make the diagnosis of chronic beryllium disease, 4 to 5 criteria must be presented. To confirm significant exposure to beryllium, all cases must include either criteria 1 or 6.

Establishing an exposure history may be difficult. Frequently, exposures occurred many years prior to a patient's medical attention. Inadequate labeling at the time of exposure and memory problems compound the difficulty. Objective information confirming exposure may be obtained by finding beryllium in biopsy specimens (usually lung and thoracic lymph nodes) or in urine. Beryllium is excreted slowly and may be found in urine up to 20 years after the last exposure to beryllium. These findings help confirm exposure only and not the presence or absence of disease related to exposure.

Criteria 2 to 5 (Table II-28) are self explanatory and have been discussed under clinical description.

Investigators working with the Beryllium Case Registry have found that tissue analysis for beryllium in lung and thoracic lymph nodes is a useful method to document beryllium exposure and to differentiate chronic beryllium disease from sarcoidosis. Using the modified Morin fluorometric method of analyzing for beryllium (reported by Walkley (29)), Sprince et al. showed that levels greater than 0.02 μg beryllium per gram dried tissue are found in 82% of the lung specimens of chronic beryllium disease cases (24). In normals and in patients with sarcoidosis, beryllium levels are all below 0.02 μg per gram dried tissue. Elevated mediastinal lymph node beryllium content has been reported by Hasan and Kazemi and is helpful in establishing a diagnosis (10). The combination of an elevated content of beryllium in tissue with compatible histopathologic changes confirms the diagnosis of chronic beryllium disease in many cases. If exposure is well documented and the non-invasive clinical criteria (criteria 2-4, Table II-28) are met, diagnosis may be made without the necessity of a biopsy of the lung or mediastinal lymph node.

Some investigators with experience in tests of cellular immunity have found other tests—namely blast transformation of lymphocytes, and tests of beryllium macrophage migration inhibition—useful in the diagnosis of chronic beryllium disease and would include these tests in the diagnostic criteria.

Mention should be made of the beryllium patch test—a skin test for documenting hypersensitivity to beryllium—reported by Curtis. This test probably has no current clinical usefulness in diagnosis because of false negatives, induction of sensitivities of previously unexposed individuals to beryllium, and the possibility of exacerbating respiratory tract involvement by application of the skin test.

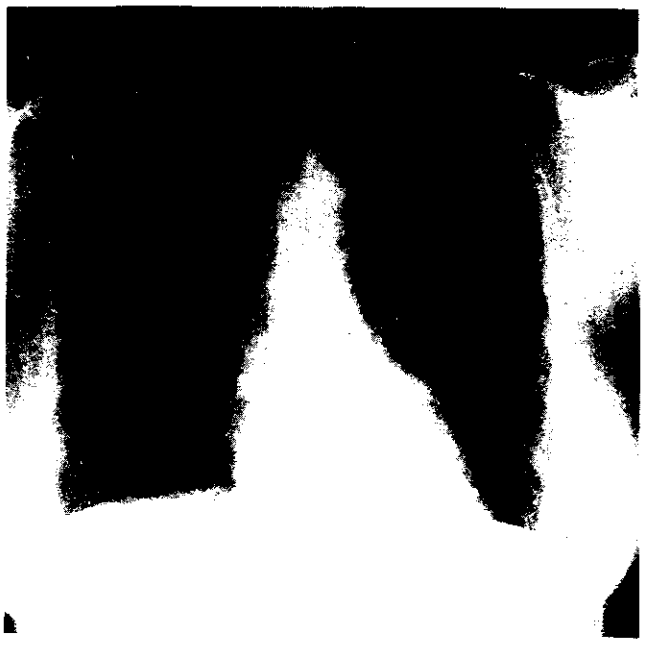

Figure II-41. Chest radiograph showing a rare presentation of chronic beryllium disease, isolated bilateral hilar lymphadenopathy. The patient is a 48-year-old woman who presented with no symptoms and with a normal physical examination. She had worked from 1940 to 1946 manufacturing fluorescent lamps. Mediastinal lymph node biopsy revealed noncaseating granulomas and an elevated beryllium content of 0.32 μg per gram dried tissue.

DIFFERENTIAL DIAGNOSIS

The diagnosis of chronic beryllium disease is frequently difficult. Other diseases which enter into differential consideration include idiopathic pulmonary fibrosis, miliary tuberculosis, fungal diseases, pulmonary hemosiderosis, lymphangitic carcinoma, hypersensitivity pneumonitis, silicosis, and other pneumoconioses. The most difficult differential is between chronic beryllium disease and sarcoidosis because these diseases share similar signs, symptoms, radiographic abnormalities, lung function findings, and histopathology.

Useful differential features between chronic beryllium disease and sarcoidosis have been recently reviewed by Sprince et al. (24). To date, uveitis, uveoparotid fever, cranial and peripheral nerve involvement, and cystic bone lesions have been reported in sarcoidosis but not in chronic beryllium disease. Complete resolution of radiographic abnormalities (common in sarcoidosis) is rare in chronic beryllium disease. The Kveim test (tissue levels of beryllium and serum angiotensin—1 converting enzyme (ACE) levels) may aid in differentiating these diseases. The Kveim test, which is positive in approximately 80% of sarcoidosis patients, has been negative in all chronic beryllium disease patients tested. Lung tissue from patients with chronic beryllium disease contains higher concentrations of beryllium than lung tissue from controls and patients with sarcoidosis. If elevated, serum ACE levels are more suggestive of sarcoidosis than chronic beryllium disease, since 48% of sarcoidosis patients have elevated ACE levels, compared with only 1 elevated level in 22 patients with chronic beryllium disease tested in a recent report by Sprince et al. (21). However, Lieberman et al. have reported elevated ACE levels in 3 of 4 patients with beryllium disease who were tested (15). Data from larger numbers of patients are needed before the usefulness of ACE levels in differential diagnosis is established.

Figure II-42. Chest radiograph from same patient presented in Figure II-41, taken three years after the initial film and showing bilateral hilar lymphadenopathy with the new finding of mild interstitial infiltrates.

PREVENTION

Control of beryllium air concentrations is the major mode of beryllium disease prevention. In the 1940's, large numbers of patients with beryllium disease were reported; their exposures occurred mainly in atomic research, beryllium extraction, and fluorescent lamp manufacturing. In 1949, the Atomic Energy Commission adopted limits for beryllium exposure in the workplace of 2 $\mu g/m^3$, averaged over an 8-hour day, and 25 $\mu g/m^3$ as the peak limit value at any one time during the day. By 1950, beryllium was discontinued from use in fluorescent lamp manufacturing and endeavors to control air concentrations of beryllium were instituted in extraction and other operations.

Reports from the Beryllium Case Registry indicate that, after 1950—probably because of reduction of beryllium air concentrations in industry—numbers of reported cases of acute and chronic beryllium disease decreased significantly.

Although standards for beryllium exposure have existed since 1949, industries where beryllium levels exceed acceptable standards have been reported in the 1970's. Technology is available to control beryllium in air and to meet currently accepted standards. Since control measures may be associated with prevention or reversal of disease, they should be instituted widely in all beryllium-producing or utilizing operations.

It has been an overall clinical impression that chronic beryllium disease does not develop in workers whose exposure to beryllium has been in compliance with the current standards. However, after viewing all available information, including data on carcinogenic effects of beryllium, OSHA has recommended a reduction to 1$\mu g/m^3$ as an 8-hour time-weighted-average with a 5 $\mu g/m^3$ ceiling value and no peak allowable standard.

The usefulness of detecting the individual worker who may develop beryllium disease on the basis of tests of delayed hypersensitivity has

no established role in prevention of disease to date.

As for acute disease, there is general agreement that controlling elevated air concentrations of beryllium has been effective in preventing its occurrence.

RESEARCH NEEDS

Scientific investigations have covered many aspects of beryllium disease, since the initial reports of the disease in the United States by Van Ordstrand et al. (28) and Hardy and Tabershaw (9). Many questions have been answered so that at this time beryllium disease has decreased in importance as a public health problem.

One remaining question which has not been satisfactorily answered to date, is that of the mechanism of disease production. The relative roles of dose-response relationships and immunologic or individual factors in the chronic disease need clarification and further longitudinal studies of workers exposed to beryllium would be useful to answer this question.

As stated previously, the discrepancies in estimates of the population at risk require further clarification.

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